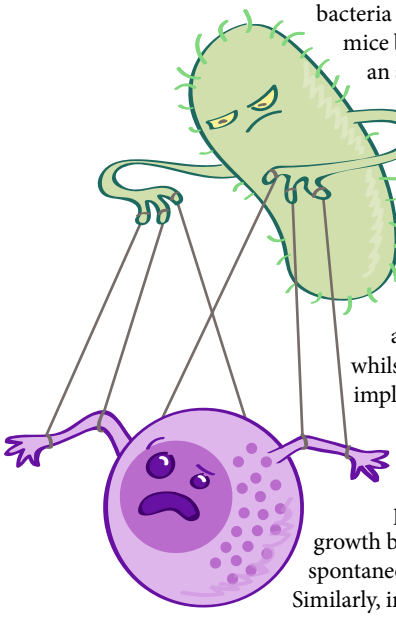
MICROBIOME

Gut microbiota bile acid metabolism controls cancer immunosurveillance

> the gut microbiota can influence the immunosurveillance of liver tumours

There is increasing evidence that the intestinal microbiota influences the progression of various cancers and has an important role in determining the efficacy of cancer immunotherapy. It is also known that antitumour immune responses can be both promoted and inhibited by the intestinal microbiota. Although the liver is exposed to gut bacterial products and metabolites by way of the portal vein, it is unclear if the gut microbiota can influence the immunosurveillance of liver tumours. Ma et al. have now demonstrated in mice that the gut microbiota can metabolize bile acids to indirectly control liver tumour growth by modulating levels of hepatic natural killer T (NKT) cells.

To investigate how the gut microbiota might shape hepatic tumour development, the authors used a transgenic mouse model of primary hepatocellular cancer (HCC) and several models of liver metastasis. The commensal gut bacteria was altered in these mice by feeding them an antibiotic cocktail (ABX, comprised of vancomycin, neomycin and primaxin). ABX-treated mice with primary HCC developed smaller and fewer tumours whilst the subcutaneous implantation of mouse EL4 lymphoma cells into ABX-treated mice did not affect primary tumour growth but did result in less spontaneous liver metastases. Similarly, intrasplenic injection of mouse B16-F1 melanoma cells into ABX-treated mice led to reduced numbers of liver metastases. However, tail vein injection of B16-F1 cells induced an increase in lung metastases. Collectively, these results suggest a liver-selective antitumour effect.



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Concomitant with the inhibition of primary liver tumour growth and liver metastases upon depletion of the gut bacterial load was a specific accumulation of hepatic NKT cells expressing CXC-chemokine receptor 6 (CXCR6). This immune cell subset had an activated phenotype and following in vivo antigen stimulation produced higher levels of interferon-γ (IFNγ). Depleting all three major T cell populations ($CD8^+$ T cells, $CD4^+$ T cells and NKT cells) with antibodies in tumour-bearing mice or using tumour-bearing mice lacking hepatic NKT cells was sufficient to eliminate the antitumour response of ABX treatment. Liver sinusoidal endothelial cells (LSECs), which represent an initial barrier for blood entering the liver from the gut, in ABX-treated mice exhibited increased surface expression of CXC-chemokine ligand 16 (CXCL16), the only ligand for CXCR6; this finding is indicative of chemokine-mediated recruitment of NKT cells to the liver parenchyma.

The gut microbiota has been reported to modulate bile acid metabolism and composition. Hypothesizing that the conversion of primary bile acids into secondary bile acids by the gut commensal bacteria could be responsible for the regulation of NKT cell accumulation, the researchers observed that exposure of LSECs to primary bile acids increased *Cxcl16* mRNA, whereas secondary bile acids had the opposite effect. This correlation was also observed in non-tumour liver tissues from patients with HCC.

To narrow down the bacterial species involved, Ma et al. found that individual antibiotic treatment with vancomycin alone caused an increase in hepatic NKT cells and a depletion of Gram-positive *Clostridium* species, known to perform the main enzymatic reaction in the generation of secondary bile acids. Importantly, colonization of vancomycin-treated mice with *Clostridium scindens* or feeding secondary bile acids to vancomycin-treated mice resulted in a decrease in hepatic NKT cells and more liver metastases.

Although hepatic NKT cells are much less prevalent in humans, mucosal-associated invariant T (MAIT) cells expressing CXCR6 are commonly found in the human liver, suggesting bile acid signals mediated by the gut microbiota to alter immune cell function and promote liver cancer could be a universal mechanism. Moreover, the discovery that altering commensal intestinal bacteria induces an antitumour effect could lead to new cancer therapies that alter the intestinal microbiome.

Anna Dart, Associate Editor
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ORIGINAL ARTICLE Ma, C. et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* **360**, eaan5931 (2018).
FURTHER READING Roy, S. & Trinchieri, G. Microbiota: a key orchestrator of cancer therapy. *Nat. Rev. Cancer* **17**, 271–285 (2017). | Zitvogel, L. et al. Anticancer effects of the microbiome and its products. *Nat. Rev. Microbiol.* **15**, 465–478 (2017).